# PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

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# PCT

## INVITATION TO PAY ADDITIONAL FEES

**(PCT Article 17(3)(a) and Rule 40.1)**

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| Applicant's or agent's file reference<br>C01037.70048 | Date of Mailing *(day/month/year)* 29 June 2004<br>PAYMENT DUE<br>within 15 days<br>from the above date of mailing |
| International application No.<br>PCT/US03/25935 | International filing date *(day/month/year)* 19 August 2003 (19.08.2003) |
| Applicant<br>COLEY PHARMACEUTICAL GROUP, INC. | |

1. This International Searching Authority

(i) considers that there are 9999999 *(number of)* inventions claimed in the international application covered by the claims indicated below/on an extra sheet:
Please See Continuation Sheet

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
Please See Continuation Sheet

(ii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.: 1-5, 12-17 (in part), 22-27 (in part)

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. The applicant is hereby invited, within the time limit indicated above, to pay the amount indicated below:

| $210.00 | X | 9999998 | = | $2,099,999,580.00 |
|---|---|---|---|---|
| Fee additional per invention | | number of additional inventions | | total amount of additional fees |

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, *i.e.*, a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☐ Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

| | |
|---|---|
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Patricia A. Duffy<br>Telephone No. 703-308-0196 |

Form PCT/ISA/206 (July 1992)

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US03/25933

This International Search Authority has found 9999999 inventions claimed in the International Application covered by the claims indicated below:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-5, 12-17 (in part) and 22-27 (in part), drawn to an immunostimulatory nucleic acid with a particular structure YZ having a phosphodiester or phosphodiester-like internucleotide linkage wherein all other internucleotide linkages are stabilized.

Group 2, claim(s)6-11, 12-17 (in part) and 22-27 (in part), drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 3, claim(s) 18 and 22-27 (in part), drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 4, claim(s) 19 and 22-27 (in part), drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 5, claim(s) 20 and 22-27 (in part), drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 6, claim(s) 20 and 22-27 (in part), drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 7, claim(s) 28-31, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 8, claim(s) 32-35, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 9, claim(s) 36-38, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 10, claim(s) 39-43, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 11, claim(s) 44-45, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 12, claim(s) 46-47, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 13, claim(s) 48, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 14, claim(s) 49-65 (in part), drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 15, claim(s) 66, drawn to drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Group 16, claim(s) 67-69, drawn to an immunostimulatory nucleic acid sequence with particularly drawn structure that does not require all other internucleotide linkages to be stabilized.

Groups 17-32, claim(s) 70-87 and 94, drawn to methods of immunostimulation of each of the technical features of Groups 1-16 defined above.

Groups 33-48, claim(s) 88-93, drawn to methods of treatment of airway remodeling using of each of the technical features of Groups 1-16 defined above.

Groups 49-64, claim(s) 95-113, drawn to method of manufacturing a medicament using of each of the technical features of Groups 1-16 defined above.

Groups 65-80, claims 114-119, drawn to use of a CG dinucletotide in the manufacture of a medicament using of each of the technical features of Groups 1-16 defined above.

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International application No.
PCT/US03/25935

Group 81, claim 120, drawn to a method of use of a olignucltotide of specific R and S chirality.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Groups 1, 17, 33, 49, 65: SEQ ID NOS:1-104 and 241.

Groups 2, 18, 34, 50, 66: SEQ ID Nos:105-240.

Groups 7, 23, 39, 55, 71: SEQ ID Nos:296-300.

Groups 8, 24, 40, 56, 72: SEQ ID Nos:301-305.

Groups 9, 25, 41, 57, 73: SEQ ID Nos:306-309.

Groups 10, 26, 42, 58, 74: SEQ ID Nos:315-317.

Groups 11, 27, 43, 59, 75: SEQ ID Nos:311-314.

Groups 12, 28, 44, 60, 76: SEQ ID Nos: 18, 319-320.

Groups 14, 30, 46, 62, 78: any of the specifically recited sequences of claims 55, 63-65.

Groups 16, 32, 48, 64, 80: any of the specifically recited sequences of claim 69.

1. This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:
The inventions listed as Groups 1-81 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the technical feature of Group I is a nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone where in the at least one pyrimidine-purine dinucleotide has a phosphodiester-like linkage and wherein all other internucleotide linkages are stabilized. Any of the art of US Patent 5,663,153; 5,723,335; 6,214,806 and 6,239,116 teach immunostimulatory sequences where at least one up to the entire sequence is stabilized using phosphorothioate bonds (see claims and discussion). A phosphorothioate bond is deemed "phosphodiester-like) and is known to stabilize nucleic acids with respect toward degradation and as such it meets the limitation of "phosphodiester-like" and "stabilized". The '153 patent discusses particular modifications of the base structure that provide for additional stability of the nucleic acid. Each of the references destroys the novelty of the oligonucleotide of claim 1 and therefore claim 1 does not define a technical feature that is "special" within the meaning of PCT Rule 13.2 because it does not define a novel contribution over the prior art. Because the technical feature of Group I is not "special" it similarly lacks unity of invention with the associated methods of use and methods of making defined by groups 17, 33, 49 and 65. As to Groups 2-16, 18-21, 34-48, 50-64, 66-81, each of the different oligonucleotides and associated methods of use and manufacture do not require the technical feature of Group I which requires all of the other internucleotide linkages to be stabilized and as such lack the structural technical feature of Group I. Similarly, for Group I, the recited species of invention, lack unity of invention because the genus is anticipated by the art set forth supra.